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Iodine Nutrition and the Risk from Radioactive Iodine: A Workshop Report in the Chernobyl Long-Term Follow-Up Study

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The major fallout of radionuclides from the nuclear power station accident at Chernobyl on 26 April, 1986, occurred in regions of Ukraine and Belarus that are believed to be moderately deficient in dietary iodine. On 17 November, 2000, in conjunction with the Ukraine-Belarus-USA study of developing thyroid disease in a cohort of individuals exposed as children, a workshop was held to review what is known about iodine nutrition in the region, how this might influence the risk of thyroid tumor formation from radioiodine, and whether and how iodine nutrition should be monitored in this long-term project. This report is a summary of the workshop proceedings. Although no precise information about iodine intake in 1986 was found, the prevalence of mild goiter in the region's children suggested iodine deficiency and urinary iodine measurements begun in 1990 indicated that mild to moderate deficiency existed. Increased thyroid iodine uptake and increased thyroid size in 1986 resulting from iodine deficiency would have had counteracting influence on the thyroid radiation dose and knowledge of these parameters is required for dose reconstruction. More problematic is the possible role of iodine deficiency in the years following the accident. Theoretically, the resulting increase in thyroid cellular activity might increase the risk of tumorigenesis but experimental or clinical evidence supporting this hypothesis is meager or absent. Despite this limitation it was considered important to monitor iodine nutrition in the cohort subjects in relation to their place of residence and over time. Methods to accomplish this were discussed.

Introduction

On 26 April 1986, an accident at the Chernobyl nuclear power station exposed the population of northern Ukraine, southern Belarus, and an adjacent region of the present Russian Federation to radioactive iodine and the risk of developing thyroid nodular disease and cancer. Beginning in 1990 an increased incidence of thyroid cancer in the children was observed (1). Recognizing this as a unique opportunity to quantify this risk the National Cancer Institute, in cooperation with the governments of the USSR, and later of Ukraine and Belarus, initiated a prospective study of a large cohort of children, the group most susceptible to radiation-induced oncogenesis (2). Iodine deficiency has been described in this geographic region and dietary iodine supplementation was discontinued in the years preceding the dissolution of the USSR in 1991. Because iodine nutrition might influence the risk, the study protocol included measurement of urinary iodine as an index of iodine intake, but concern arose as to its value for a study in which screening began 11 years after the accident. On 17 November 2000 a workshop was held in Rockville, Maryland, to address the following questions: (1) What is known about iodine intake in the region at the time of the accident and in the succeeding years? (2) How might iodine nutrition influence the oncogenic risk from radioiodine at the time of exposure and long after the event? (3) Should iodine intake be evaluated in the thyroid study and, if so, by what method? This report is a summary of the proceedings of the workshop.

Iodine Nutrition in Ukraine and Belarus

Goiter was common in the area and investigations into iodine levels in soil and water in the late 1940s suggested that much of the goiter was due to iodine deficiency (3). In the Volyn Oblast of northern Ukraine, goiter was present in 31%

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of adults and 48% of schoolchildren. This was reduced in 1951 to 20% and 27%, respectively, after 5 years of distributing iodine supplements (3). In 1958 Aber (4) was optimistic that goiter among children would be "liquidated" within "the sixth Five Year Plan." Reports (4,5) state that endemic goiter was eradicated in Ukraine in the late 1960s, but reduced attention was subsequently given to iodine supplementation and distribution. By 1990, 50% of the salt was not iodized and there had been increasing incidence of goiter each year, but the prevalence was not stated. In Gomelkaya, Belarus, goiter was present in 14% of adults and 21% of schoolchildren in 1957; the prevalence had decreased by 1985, but increased again in 1986 (5). The incidence was reported as increasing in each decade from 1970 to 1990 but the prevalence in any of these years was not stated. These reports do not clarify what the prevalence of goiter was in Ukraine and Belarus in 1986, the year of the accident, but only indicate that it had been increasing. Apparently no measurements of iodine excretion in urine were reported between 1986 and 1990.

Beginning in 1990, urinary iodine content was investigated in the Chernobyl area by several groups. Bolshova et al. (6) reported on 100 children in northern Ukraine; 29 of them had 24-hour collections and the remainder random samples. The median concentration was 50 μg/L. Ashizawa et al. (7) reported on a study of 5,710 children in Ukrainian, Belarusian and Russian regions near Chernobyl between 1991 and 1996. Median urine iodine concentration in casual samples from five regions ranged from 39 to 177 μg/L. Reports on casual urine samples in Belarus obtained from 1,680 children between 1990 and 1994 (8) and from 11,562 children between 1995 and 1998 (9) were similar and median concentrations ranged from 27 to 113 μg/L in different regions. According to ICCIDD/WHO/UNICEF criteria, all Belarusian oblasts have mild or moderate iodine deficiency (10). By median urinary iodine concentration, adequate iodine nutrition is more than 100 μg/L, mild iodine deficiency 50 to 99 μg/L, moderate deficiency 20 to 49 μg/L, severe deficiency less than 20 μg/L (10). Of interest, Gomel Oblast, the region with the highest prevalence of post-Chernobyl childhood thyroid cancer, may have had milder iodine deficiency than other regions in Belarus. In the study by Ashizawa et al. (7) urinary iodine in Gomel indicated that iodine intake was optimal whereas Mityukova et al. (8) and Arinchin et al (9) reported mild iodine deficiency.

Thyroid enlargement, another indicator of iodine deficiency in children, was evaluated in the latter studies. By ICCIDD/WHO/UNICEF criteria (10) adequate iodine nutrition is indicated by $<$5% goiters in school children, mild deficiency by 5–19.9%, moderate deficiency by 20% to 29.9%, severe deficiency by greater than 30%. Both goiter and increased serum thyroglobulin are indicators of iodine deficiency over an extended period of time (10). Based on ultrasound examination, Ashizawa et al. (7) reported a goiter prevalence of 18% to 54% while Arinchin et al. (9) reported a prevalence of 6 to 28%. The prevalence in Gomel was 22% and 6%, respectively, in these two studies. The Arinchin study used the 1997 WHO normative data from Europe (11). Subsequent work has concluded that technical differences in operation resulted in a systematic over-estimation of thyroid volume for iodine-sufficient children, and should be adjusted by a provisional "correction factor" of 0.346 (12). The prevalence of goiter in the Chernobyl area also depends on the availability of age-related normal thyroid volumes in a region with normal iodine intake; this was apparently the case in the study by Ashizawa et al. (7). Arinchin et al. (9) reported a prevalence of goiter based on palpation that ranged from 23% to 44%, and was 23% in Gomel.

Preliminary data on iodine concentration in casual urine specimens collected from cohort members in Ukraine and Belarus, beginning in 1997, were presented at the workshop. These will be reported in detail when the first round of screening has been completed in the approximately 25,000 cohort members. Thus far the data are quite similar to those reported above. The regions included in the cohort study are characterized by mild to moderate iodine deficiency; many of the regions are moderately deficient but Gomel is only mildly deficient. In both countries, rural residents tend to have lower urinary iodine excretion than city residents and there are seasonal variations. There is suggestive evidence that iodine nutrition may be improving in some areas and it is expected that household salt will be required to be fortified with iodine in the near future in both countries.

Iodine Nutrition and Thyroid Tumorigenesis

There are two ways that iodine nutrition might affect the tumorigenic or oncogenic risk from exposure to radioactive iodine: by influencing the radiation dose received by the gland and by altering the response to the irradiation. The first is a short-term effect operative only during the early hours and days after exposure. The second is a long-term effect that could operate throughout the life of the irradiated individual. By tumorigenesis, we mean the induction of benign as well as malignant lesions, since both are known to result from external thyroid radiation (13).

The influence of iodine intake on the thyroid radiation dose is relatively straightforward. From a number of studies after exposure to external radiation it is well established that tumor induction is directly related to the dose, modified by age and gender (14). The relative effectiveness of the dose derived from external radiation and that derived from radioiodine, however, especially from ^{131}I in humans, is uncertain (15), which explains the importance of the Chernobyl cohort study. But there are additional, biological parameters to consider in the case of internal radiation that are strongly affected by iodine nutrition; these include the effects on radioiodine uptake, on thyroid volume and, possibly, on the response to the received radiation dose. Although it is known that several iodine radionuclides with very different decay rates were released by the accident (16), all would be affected by the same biological parameters, even if not in an exactly parallel manner.

The radiation dose delivered by a unit quantity of radioiodine is directly proportional to the amount ingested or inhaled, to the fraction of this amount taken up by the thyroid gland, and to the duration of its retention. The dose is inversely proportional to the size of the gland in which the radionuclide is deposited. To maintain homeostasis of the thyroid system, iodine deficiency and its tendency to decrease thyroid hormone production results in several corrective adjustments. These include an increase in fractional uptake leading to an increased radiation dose, and an increase in thyroid size leading to a decreased radiation dose.

Both of these changes develop slowly when iodine intake is reduced (17). When the iodine deficiency is corrected, the increase in iodine ingestion results in a restoration of normal thyroid iodine uptake but the goiter usually does not resolve completely. Iodine deficiency also can cause a decrease in the retention time of radioiodine in the gland. Because the secretion half-time is usually much longer than the radionuclide decay, even in the case of ^{131}I with its 8-day half-life, the change in radioiodine retention is much less important than the changes in radioiodine uptake and thyroid volume.

The influence of iodine nutrition on the response of the thyroid to irradiation is less certain, and the available data are restricted to animal experimentation. Many of these studies employed antithyroid drugs, with or without a low iodine diet, as an additional or alternative method to induce an increase in thyrotropin (TSH) secretion. Iodine deficiency leads to TSH-based stimulation of the thyroid resulting in cellular hypertrophy and hyperplasia (18). Severe and prolonged deficiency in rats can result in various thyroid tumors including papillary carcinoma (19,20). Partial thyroidectomy also results in TSH stimulation and leads to tumor formation (21,22). Radioiodine administered to rats and mice causes thyroid tumors (23) and the yield is influenced by the level of TSH stimulation [e.g., see Nadler et al. [23]]. Most of these experiments were short-term, and only in one (24) was the stimulation begun subsequent to the radiation. Even in that case the interval between radiation and stimulation was only 24 hours. To our knowledge, no experiments have been reported in which animals treated with ^{131}I were placed on a low iodine diet long after exposure to the radiation.

It is difficult to relate these animal experiments to radiation-exposed humans, and to the Chernobyl population in particular. The experimental iodine deficiency was usually more severe, antithyroid drugs were often given, thyroid tumors in rodents usually do not resemble the papillary cancers that are the typical outcome of radiation in humans (25) and, as discussed above, the experiments were usually short-term. One study of patients who had been exposed to external radiation, however, suggests that uncontrolled thyroid stimulation might affect the outcome. Fogelfeld et al. [26] found that patients who had a partial thyroidectomy for benign nodular disease and had not been given thyroid hormone replacement therapy developed significantly more thyroid nodules than did patients receiving thyroid hormone. Although a significant difference in development of thyroid cancers was not observed, this experience, coupled with the animal experiments, suggests caution in rejecting the possibility that iodine nutrition long after exposure might affect thyroid cancer risk. Theoretically, increased cell division in an irradiated thyroid gland could lead to errors in gene replication with production of an oncogene or reduction of a tumor suppressor gene, and chronic thyrocyte stimulation might cause other changes that affect how the cell responds to radiation. There is insufficient experimental evidence, however, to support this supposition.

Many clinical studies have examined the relationship between iodine nutrition and thyroid neoplasia, although these are not related to radiation exposure. It is well established that iodine deficiency is associated with an increased incidence of thyroid nodules [e.g., see Gutekunst et al. [27]]. Most studies also show that the ratio of follicular to papillary cancers is higher in iodine-deficient regions. Estimates of absolute incidences from two Sicilian communities with different iodine intakes found more follicular and anaplastic cancers, but fewer papillary cancers, in the iodine-deficient region (28). Several studies relate higher dietary iodine to increases in the incidence of papillary cancer (29–31). Other reports examine these relationships, with varying conclusions. The available studies are limited by inadequate data on iodine nutrition, frequent lack of quantitative anatomical data, and uncertainties about validity of their population comparisons, effects of changing iodine nutrition and other factors such as radiation and discovery. Overall, they suggest that iodine deficiency increases the incidence of thyroid nodules and follicular cancer, while iodine sufficiency and excess are associated with more papillary cancer and more autoimmune thyroid disease. It is clear that iodine nutrition may affect the incidence of thyroid neoplasia, and should be carefully monitored in any long-term follow-up study.

Determining Iodine Nutrition in the Chernobyl Study Cohort

As discussed in the first section of this summary, there is no precise information available about iodine nutrition in the cohort at the time of the accident. On the other hand, it appears that little has changed since that time; thus it is reasonable to use current information on age-related thyroid size in regions where iodine intake has been similar to that in the heavily exposed areas. Because a significant increase in iodized salt availability is anticipated, these data should be collected soon. Knowledge about iodine uptake is less important because a requirement for inclusion in the cohort was that each member must have had a thyroid radioactivity measurement after the accident. This parameter is being used in radiation dose reconstruction (32). An important additional factor is whether high-dose potassium iodide (KI) was used to block radioiodine uptake in the period immediately after the accident. Administration of KI was erratic (33) and is an important feature in the dosimetry questionnaire that is administered to all cohort members. The screening examinations of the cohort have included determination of thyroid size by palpation and ultrasonography and measurement of serum thyroglobulin as indices of past iodine nutrition. Analysis of iodine in casual urine specimens is included as an index of current iodine nutrition. In this section of the workshop, consideration was given to whether this initial evaluation of current iodine nutrition was adequate and whether changes should be made if evaluation were to be continued as the cohort study progresses.

Urinary iodine in a casual urine sample is the single most useful marker for community iodine nutrition because over 90% of ingested iodine eventually appears in urine, the samples are easy to obtain in the field, and the analytical methods are inexpensive and easily mastered (10). Furthermore, urine iodine reflects iodine excess as well as deficiency. In a community survey the goal is to choose representative samples of the target population and to survey the smallest number of individuals assuring validity and adequate precision. One approach is to select 30 clusters or survey sites from a listing of all sites (such as schools) adjusted for population size and to randomly sample 10 to 30 individuals in each

site. Numerous studies have established criteria for evaluating community iodine nutrition in this way (34,35).

By appropriate sampling, the average iodine nutrition in the cohort could be determined without examining each individual member. Aggregate data, however, would have limited usefulness for risk analysis and must be used cautiously. Using individual data, on the other hand, can distort conclusions unless the index value has a dependent relationship with the true value (36). Use of aggregate data for characterizing iodine nutritional status or thyroid function results in a type of measurement error known as "Berkson error." Under a presumed linear dose-response relationship, estimates of exposure effects are approximately unbiased although their estimates of variance are increased. In the case of the cohort study we are probably dealing with a classical error, where the error in risk estimate will depend on the degree of variability in the relationship between the casual urine value and the true value.

A closer estimate of the true value would be obtained with 24-hour urine collection, but this is difficult to accomplish in a large population, especially under field conditions. Another consideration is whether collection of a fasting urine specimen would reduce the error. This was the conclusion of a study by Thomson et al. (37) that demonstrated a better correlation between fasting urine samples and 24-hour collections compared to casual urine samples. A recent study from Denmark measured 24-hour urine iodine samples and compared them with estimates from casual samples during the same day, recorded as iodine concentration, as iodine per gram creatinine, or as iodine-to-creatinine ratio adjusted for expected creatinine excretion in the individual (38). The authors concluded that the latter was closest to the 24-hour value, although extrapolating the micrograms iodine per liter to 1.5 liters urine per day (the average adult 24-hour volume) gives a value close to the one recorded at 24-hours. The iodine concentration in casual urine samples has been adequate for epidemiological studies of large groups. For studying individuals, relation to the creatinine concentration is desirable. A caveat is that poor general nutrition can lower the urinary creatinine and artifactually elevate the iodine to creatinine ratio.

Conclusions

Iodine nutritional status at the time of exposure to radioactive iodine strongly affects the thyroid radiation dose because of its effect on thyroid iodine uptake and thyroid volume.

Iodine deficiency late after exposure to radioiodine, and the resulting increase in TSH, may increase the risk of tumorigenesis and oncogenesis by increasing the rate of cell division and enhancing cell growth, but there are no relevant experimental data in humans and the supporting data in animals are of limited value.

Iodine nutrition around Chernobyl is mildly to moderately deficient, but the only available data in 1986 are based on the prevalence of goiter. There are significant regional variations, and iodine intake is expected to change in the near future as Belarus and Ukraine adopt measures to supplement dietary iodine.

Thyroid gland volume and serum thyroglobulin concentration are indicators of iodine nutrition over the previous several years.

Urinary iodine analysis is the preferred method to evaluate current iodine nutrition, and analytic methods are simple and inexpensive. Casual urine specimens are adequate for population studies but not for individual subjects. It may, however, be possible to utilize individual measurements in risk analysis if the error can be minimized. Independent of this, urinary iodine helps to define iodine nutrition in the cohort as a group.

The workshop recommended continuing attention to iodine nutrition in long-term studies such as these in view of its known and its potential influence on the development of benign and malignant thyroid tumors in response to irradiation or other insults.

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